REMARKS

Applicants acknowledge that the Examiner has made final the restriction of the pending claims into Groups I-II. Applicants maintain their election of Group II. Consistent with that election, applicants have canceled claims 1, 18 and 20 directed to the non-elected subject matter without prejudice and without waiver of their right to file for and obtain claims directed to any non-elected subject matter in divisional and continuing applications which claim priority from this application.

Applicants have amended claims 5-7, 9 and 11-12 to cancel the dependency from claim 1, which has been canceled.

Applicants have amended claim 13 to correct an indavertent typographical error in the recitation of 12-hydroxyeicosatetraenoic acid.

None of the amendments introduces new matter.

Applicants address the Examiner's objections and rejections below.

The Objections

Specification: pages 8-12

The Examiner has objected to The Brief Description of the Drawings for referring to colored staining in the drawings. The Examiner states that because the drawings were submitted in black and white, they cannot be analyzed for color.

Applicants have amended the specification to recite staining rather than blue staining. Accordingly, the Examiner's objection has been obviated.

Specification: page 42

The Examiner has objected to the specification for improper disclosure of amino acid sequences without a respective sequence identifier.

Applicants have amended page 42, line 11 of the specification to recite SEQ ID NOs 11 and 12 following the references to COP5 and COP7, respectively. Applicants also submit herewith an amended Sequence Listing. In the amended Sequence Listing, applicants have added SEQ ID NOs 11 and 12 to correspond to the COP5 and COP7 sequences, respectively.

In accordance with 37 C.F.R. § 1.821, applicants submit concurrently herewith an amended Sequence Listing in computer readable form together with a Statement Under 37 C.F.R. §§ 1.825(a) and (b) that the paper and computer readable copies of the amended Sequence Listing are the same and do not include new matter.

Claim 13

The Examiner has objected to claim 13 stating that the recitation of "selected from the group consisting acidic" should be amended to recite "selected from the group consisting of acidic". Applicants have amended claim 13 according to the Examiner's suggestion, thus obviating the objection.

Claims 5-7, 9 and 11-12

The Examiner has objected to claims 5-7, 9 and 11-12 as being dependent from non-elected claim 1.

Applicants have amended claims 5-7, 9 and 11-12 to cancel their dependence from claim 1. Accordingly, the Examiner's objection has been obviated.

The Rejections

35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 6, 8, 10 and 13-16 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner contends that while the

specification is enabling for combining specific morphogenic proteins with morphogenic protein stimulatory factors to improve angiogenesis, it is not enabling for combining amino acid sequence variants of morphogenic proteins and or amino acid sequence variants of morphogenic protein stimulatory factors.

Applicants have amended claims 6, 8 and 10 to recite that the amino acid variants of the morphogenic proteins have angiogenic activity. Applicants have also amended claims 13-16 to recite that the amino acid variants of the morphogenic protein stimulatory factors improve the angiogenic inductive activity of the morphogenic protein. It would be routine for one of skill in the art to determine whether an amino acid variant of a morphogenic protein is capable of inducing angiogenesis or whether an amino acid variant of a morphogenic protein stimulatory factor is capable of improving the angiogenic inductive activity of a morphogenic protein. Applicants have provided examples of assays (see examples 1-3 on pages 51-53 of the specification) which may be used to determine whether an amino acid variant of a morphogenic protein is capable of inducing angiogenesis or whether an amino acid variant of a morphogenic protein stimulatory factor is capable of improving the angiogenic inductive activity of a morphogenic protein. Accordingly applicants request that the Examiner withdraw the enablement rejection with respect to claims 6, 8, 10 and 13-16.

35 U.S.C. § 102(b)

The Examiner has rejected claims 2, 4-6, 9-14,16, 17 and 19 under 35 U.S.C. § 102(b) as being anticipated by Duneas et al., Growth Factors, 15, pp. 259-277 (1998) ("Duneas"). The Examiner contends that Duneas teaches the simultaneous administration of a

morphogenic protein (OP1) and a morphogenic protein stimulatory factor (TGF-β) to a target locus wherein the target locus is a vascular tissue defect. The Examiner further contends that Duneas teaches that the two proteins interact synergistically and that the data "suggests that the two morphogens interact synergistically to induce angiogenesis and vascular invasion". Applicants traverse.

Applicants respectfully submit that Duneas teaches that OP-1 and TGF-β1 act synergistically to induce large ossicle formation in the rectus abdominus. The data presented in Duneas do not demonstrate that treatment with OP-1 and TGF-β1 results in enhanced vascularization over TGF-β1 or OP-1 alone. Duneas merely demonstrates that vascularization occurs upon treatment with OP-1 and TGF-β1. Although Duneas states that the "many-fold increase in type IV collagen mRNA synthesis over hOP-1 and pTGF-β1 suggests that the two morphogens interact synergistically to induce angiogenesis", nothing in Duneas demonstrates that type IV collagen expression is required for angiogenesis. At best, the data in Duneas suggests that there may be a correlation between collagen IV mRNA expression and enhanced vascularization.

The claims of the present invention, on the other hand, recite a method for improving the angiogenic inductive activity of a morphogenic protein by coadministering a morphogenic protein stimulatory factor. Duneas does not demonstrate that the angiogenic inductive activity of a morphogenic protein is improved by coadministering a morphogenic protein stimulatory factor. Accordingly, applicants request that the Examiner withdraw this rejection.

35 U.S.C. § 102(e)

The Examiner has rejected claims 2-5, 7 and 12-15 under 35 U.S.C.§ 102(e) as being anticipated by Goldberg et al. (United States Patent 6,013,624) ("Goldberg") as evidenced by Amano et al. (Arch. Oral Biol., 44, pp.935-946 (1999)) ("Amano"). The Examiner contends that Goldberg teaches a method for improving the angiogenic inductive activity of a morphogenic protein, scatter factor, by coadministering a morphogenic protein stimulatory factor, FGF. The Examiner further contends that Amano teaches that scatter factor, which is also known as hepatocyte growth factor is osteogenic. Applicants traverse.

Applicants respectfully submit that the morphogenic proteins of this invention are defined as the TGF-β superfamily of proteins. It is the morphogenic protein stimulatory factors that are defined to include hormones, cytokines, and growth factors, including hepatocyte growth factor and FGFs.

Goldberg describes the enhancement of angiogenesis by administering scatter factor (hepatocyte growth factor) in combination with FGF. Both scatter factor (hepatocyte growth factor) and FGF are defined in the instant application as morphogenic protein stimulatory factors and neither protein is included in the definition of a morphogenic protein. Unlike the claims of the instant application which recite the use of a morphogenic protein and a morphogenic protein stimulatory factor for the enhancement of angiogenesis, Goldberg describes the use of two morphogenic protein stimulatory factors, but no morphogenic protein, for the enhancement of angiogenesis. Accordingly, applicants request that the Examiner reconsider this novelty rejection.

35 U.S.C. § 103(a)

The Examiner has rejected claims 2-5, 7, 12-15, 17 and 19 as being obvious over Goldberg as evidenced by Amano. The Examiner contends that "[i]t would have been prima facie obvious to one of skill in the art at the time the invention was made to administer the morphogenic protein (scatter factor) and the morphogenic protein stimulatory factor (FGF) 'simultaneously' to a target locus because Golberg teaches that angiogenesis can be enhanced by administering scatter factor in combination with a growth factor". Applicants traverse.

As already described above, Golberg describes the use of two morphogenic protein stimulatory factors to enhance angiogenesis, whereas the claims of the instant application recite the use of a morphogenic protein and a morphogenic protein stimulatory factor to enhance angiogenesis. Nowhere in Goldberg, alone or in combination with Amano, is there a suggestion or teaching that a morphogenic protein and a morphogenic protein stimulatory factor as defined in this application can be used to enhance angiogenesis. Accordingly, applicants request that the Examiner withdraw the obviousness rejection.

CONCLUSION

For all the above reasons, applicants request that the Examiner withdraw all outstanding objections and rejections and grant allowance of the pending claims.

The Examiner is invited to telephone applicants' representatives regarding any matter that may be handled

by telephone to expedite allowance of the pending claims.

Respectfully submitted,

Karen Mangasarian

James F. Haley, Jr. (Reg. No. 27,794)
Karen Mangasarian (Reg. No. 43,772)
Attorneys for Applicants
c/o FISH & NEAVE
1251 Avenue of the Americas
New York, New York 10020
Tel.: (212) 596-9000

I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: ASSISTANT COMMISSIONER FOR PATENTS WASHINGTON, D.C. 20231 on

September 19, 2001

Claire M. Spinell

Signature of Person Signing

APPENDIX OF SPECIFICATION AMENDMENTS

IN THE SPECIFICATION

Paragraph spanning pages 8-9

Figure 3. Cross section of a typical control-treated chick chorioallantoic membrane (CAM) following exposure to 500 ng of bovine serum albumin (BSA) for 5 days. The area in the vicinity of the beads shows normal structures with thin ectodermal (ec) and endodermal (en) epithelia enclosing the mesodermal (me) stroma. The original positions of some gel beads (g) are distinguishable by indentations in the ectodermal surface of the CAM. The mesoderm consists primarily of sparse and loosely arranged fibroblasts in wide intercellular spaces. Occasional large blood vessels (bv) with nucleated erythrocytes are observed in the mesoderm. The ectoderm exhibits normal development of the intradermal capillaries (iec). [Blue staining] Stained collagen fibers are sparsely distributed in some regions within the mesoderm. Vestiges of gelatin (gl) remain between the beads and in the regions between the beads and the stratified ectoderm. Scale bar = 50 μm.

Page 9, lines 11-24

Figure 4. Histological response of chick chorioallantoic membrane (CAM) after the application of 20 ng pTGF-β1. There is a distinct thickening of the mesoderm (me) and extensive stratification of the endoderm (en). A widespread proliferation of capillaries (ca) is observed throughout the mesoderm. A discrete accumulation and condensation of the fibrous connective tissue (ct), which is mainly localized in the endodermal portion of the mesoderm, accompanies the increase in the

number of capillaries. [Blue staining] Stained collagen fibers are densely spread in the condensed fibrous tissue within the mesoderm in the locality of the reaction center. Sloughing of the endodermal cells (arrowhead) is observed. Scale bar = 100 μm.

Paragraph panning pages 9-10

Figure 5. Histological response of chick chorioallantoic membrane (CAM) after exposure to 500 ng of bFGF. There is a distinct thickening of the mesoderm (me) and extensive stratification of both the ectoderm (ec) and endoderm (en). Dense accumulations of fibroblast-rich connective tissue (ct) are localized in areas close to both the ectodermal and the endodermal portions of the mesoderm. Capillaries (ca), as well as a large number of blue-staining collagen fibers, are spread widely throughout the reactive mesoderm. Clusters of cells (cd) with a similar appearance to the stratified ectoderm are embedded within the mesoderm. [Blue staining] Stained collagen fibers are densely spread in the condensed fibrous tissue within the mesoderm in the locality of the reaction centers and finely spread in the central portion of the mesoderm. Remnants of gelatin (gl) are located between the beads and in the vicinity of the ectoderm. Scale bar = 100 μm.

Page 11, lines 6-16

Figure 7. Histological reaction of a chick chorioallantoic membrane (CAM) after the application of a combination of hOP-1/bFGF (100/100 ng). Numerous distended blood vessels (bv) and capillaries (ca) with nucleated erythroytes are widely distributed within the oedematous mesoderm (me). The fibrous connective tissue (ct), consisting of [blue staining] stained collagen

fibers, is very dense and widely distributed throughout the thickness of the reactive mesoderm. The endoderm (en) and the ectoderm (ec) (not in this section) thickened by stratification. Scale bar = 50 µm.

Paragaraph spanning pages 11-12

Figure 8. Chick chorioallantoic membrane (CAM) response following exposure to hOP-1/pTGF-β1. (A) hOP-1/pTGF-β1 (100/5 ng): there is a very marked thickening of all the three layers of the CAM. The multilayered endoderm (en) exhibits a villi-like pattern. Widespread capillaries (ca) and fibrous tissue (ct) are located over the entire reactive mesoderm (me) containing numerous distended blood vessels (bv). [Blue staining] Stained collagen fibers are densely spread in the condensed fibrous tissue within the mesoderm in the locality of the areas adjacent to the ecto- and endoderm and finely spread in the central portion of the mesoderm. Clusters of cells (cd) with a similar appearance to the stratified ectoderm are embedded within the mesoderm. Sloughing of the endoderm (arrowheads) is clearly visible. Scale bar = 50 µm. (B) hOP-1/pTGF-β1 (100/20 ng): There is extensive fibrous tissue (ct) condensation and prominently high number of capillaries (ca). Evidence of bead (g) encapsulation is clearly noticeable. The dense connective tissue fibers including the blue-staining collagen, are aligned in the region skirting the zone of encapsulated beads. The multilayered endoderm (en) is villi-like and the thickened ectoderm is vessel-free. Sloughing of the endoderm (arrowhead) is clearly visible. Scale bar = 100 µm.

Page 42, lines 11-20

The amino acid sequences of COP5 (SEQ ID NO:11) and COP7 (SEQ ID NO:12) are shown below, as set forth in Oppermann et al., U. S. Patent Nos. 5,011,691 and 5,324,819, which are incorporated herein by reference:

COP5 LYVDFS-DVGW**D**DWIVAPPGY**Q**AFYCHGECPFPLAD

COP7 LYVDFS-DVGW**N**DWIVAPPGY**H**AFYCHGECPFPLAD

COP5 H**F**NSTN--H-AVVQTLVNSVNSKI--PKACCVPTELSA

COP7 H**L**NSTN--H-AVVQTLVNSVNSKI--PKACCVPTELSA

COP5 ISMLYLDENEKVVLKYNQEMVVEGCGCR

COP7 ISMLYLDENEKVVLKYNQEMVVEGCGCR

APPENDIX OF CLAIM AMENDMENTS

5. (Amended) The method according to any one of claims [1] 2 to 4, wherein the morphogenic protein is an osteogenic protein that is capable of inducing angiogenesis.

6. (Amended) The method according to any one of claims [1] 2 to 4, wherein the morphogenic protein comprises an amino acid sequence selected from the group consisting of BMP-3, BMP-4, BMP-5, BMP-6, OP-1 (BMP-7), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, COP-5, COP-7 and an amino acid sequence variant thereof, wherein the amino acid sequence variant has angiogenic activity.

7. (Amended) The method according to any one of claims [1] 2 to 4, wherein the morphogenic protein is a monomeric species.

8. (Amended) The method according to claim 7, wherein the monomeric species is selected from the group consisting of OP-1, BMP-5, BMP-6, BMP-8, GDF-6, GDF-7 and amino acid sequence variants thereof, wherein the amino acid sequence variant has angiogenic activity.

9. (Amended) The method according to any one of claims [1] 2 to 4, wherein the morphogenic protein comprises a disulfide bonded dimeric species.

10. (Amended) The method according to claim 9, wherein the dimeric species comprises a polypeptide selected from the group consisting of OP-1, BMP-5, BMP-6, BMP-8, GDF-6, GDF-7 and amino acid sequence variants thereof, wherein the amino acid sequence variant has angiogenic activity.

11. (Amended) The method according to any one of claims [1] 2 to 4, wherein the morphogenic protein is OP-1.

12. (Amended) The method according to any one of claims [1] 2 to 4, wherein the morphogenic protein is produced by the expression of a recombinant DNA molecule in a host cell.

13. (Amended) The method according to any one of claims 2 to 4, wherein the morphogenic protein stimulatory factor comprises at least one compound selected from the group consisting of acidic fibroblast growth factor (aFGF), basic fibroblast growth factor FGF (bFGF), transforming growth factor-β (TGF-β), transforming growth factor-α (TGF-α), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), endothelial cell growth factor (ECGF), insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), platelet activating factor (PAF), interleukin-8 (IL-8), placental growth factor (PGF), proliferin, B61, soluble vascular cell adhesion molecule-1 (SVCAM-1), soluble E-selectin, ephrin, [12-hydorxyeicosatetraenoic acid] 12-hydroxyeicosatetraenoic acid, tat protein of HIV-1, angiogenin, prostaglandin and amino acid sequence variants thereof, wherein the amino acid sequence variant of the morphogenic protein stimulatory factor improves the angiogenic inductive activity of the morphogenic protein.

14. (Amended) The method according to any one of claims 2 to 4, wherein the morphogenic protein stimulatory factor comprises at least one compound selected from the group consisting of basic fibroblast growth factor (bFGF), platelet derived transforming growth factor-β1 (TGF-β1) and amino acid sequence variants thereof,

wherein the amino acid sequence variant of the morphogenic protein stimulatory factor improves the angiogenic inductive activity of the morphogenic protein.

15. (Amended) The method according to any one of claims 2 to 4, wherein the morphogenic protein stimulatory factor is selected from the group consisting of basic fibroblast growth factor (bFGF) and amino acid sequence variants thereof, wherein the amino acid sequence variant of the morphogenic protein stimulatory factor improves the angiogenic inductive activity of the morphogenic protein.

16. (Amended) The method according to any one of claims 2 to 4, wherein the morphogenic protein stimulatory factor is selected from the group consisting of platelet derived transforming growth factor-β1 (TGF-β1) and amino acid sequence variants thereof, wherein the amino acid sequence variant of the morphogenic protein stimulatory factor improves the angiogenic inductive activity of the morphogenic protein.